Biliary Atresia in Children: Update on Disease Mechanism, Therapies, and Patient Outcomes

Swati Antala and Sarah A. Taylor

Biliary atresia is a rare disease but remains the most common indication for pediatric liver transplantation as there are no effective medical therapies to slow progression after diagnosis. Variable contribution of genetic, immune, and environmental factors contributes to disease heterogeneity among patients with biliary atresia. Gaining a deeper understanding of the disease mechanism will help to develop targeted medical therapies and improve patient outcomes.

Alagille Syndrome: Current Understanding of Pathogenesis, and Challenges in Diagnosis and Management

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Alagille syndrome (ALGS) is a complex heterogeneous disease with a wide array of clinical manifestations in association with cholestatic liver disease. Major clinical and genetic advancements have taken place since its first description in 1969. However, clinicians continue to face considerable challenges in the management of ALGS, particularly in the absence of targeted molecular therapies. In this article, we provide an overview of the broad ALGS phenotype, current approaches to diagnosis and with particular focus on key clinical challenges encountered in the management of these patients.

Overview of Progressive Familial Intrahepatic Cholestasis

Sara Hassan and Paula Hertel

Bile acid transport and secretion is a complex physiologic process, of which disruption at any step can lead to progressive intrahepatic cholestasis (PFIC). The first described PFIC disorders were originally named as such before identification of a genetic cause. However, advances in clinical molecular genetics have led to the identification of several disorders that can cause these monogenic inherited cholestasis syndromes, and they are now increasingly referred to by the affected protein causing disease. The list of PFIC disorders is expected to grow as more causative genes are discovered. Here forth, we present a comprehensive overview of known PFIC disorders.

Alpha-1 Antitrypsin Deficiency Liver Disease

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Liver disease in homozygous ZZ alpha-1 antitrypsin (AAT) deficiency occurs due to the accumulation of large quantities of AAT mutant Z protein polymers in the liver. The mutant Z protein folds improperly during
biogenesis and is retained within the hepatocytes rather than appropriately secreted. These intracellular polymers trigger an injury cascade, which leads to liver injury. However, the clinical liver disease is highly variable and not all patients with this same homozygous ZZ genotype develop liver disease. Evidence suggests that genetic determinants of intracellular protein processing, among other unidentified genetic and environmental factors, likely play a role in liver disease susceptibility. Advancements made in development of new treatment strategies using siRNA technology, and other novel approaches, are promising, and multiple human liver disease trials are underway.

Hepatitis B and C in Children
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Hepatitis B and hepatitis C are a global burden and underscore the impact of preventable acute and chronic diseases on personal as well as population level health. Caring for pediatric patients with hepatitis B and C requires a deep understanding of the pathophysiology of viral processes. Insight into the epidemiology, transmission, and surveillance of these infections is critical to prevention and therapy. Extensive research in recent years has created a growing number of treatments, changing the landscape of the medical field’s approach to the viral hepatitis pandemic.

Mitochondrial Hepatopathy
Mary Ayers, Simon P. Horslen, Anna María Gómez, and James E. Squires

Mitochondrial hepatopathies are a subset of mitochondrial diseases defined by primary dysfunction of hepatocyte mitochondria leading to a phenotype of hepatocyte cell injury, steatosis, or liver failure. Increasingly, the diagnosis is established by new sequencing approaches that combine analysis of both nuclear DNA and mitochondrial DNA and allow for timely diagnosis in most patients. Despite advances in diagnostics, for most affected children their disorders are relentlessly progressive, and result in substantial morbidity and mortality. Treatment remains mainly supportive; however, novel therapeutics and a more definitive role for liver transplantation hold promise for affected children.

Nonalcoholic Steatohepatitis in Children
Stavra A. Xanthakos

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in children. Although environmental factors are major contributors to early onset, children have both shared and unique genetic risk alleles as compared with adults with NAFLD. Treatment relies on reducing environmental risk factors, but many children have persistent disease. No medications are approved specifically for the treatment of NAFLD, but some anti-obesity or diabetes treatments may be beneficial. Pediatric NAFLD increases the risk of diabetes and other cardiovascular risk factors. Long-term prospective studies are needed to determine the long-term risk of hepatic and non-hepatic morbidity and mortality in adulthood.
Pediatric acute liver failure (PALF) is a complex, unpredictable, often rapidly progressive, potentially devastating clinical syndrome that occurs in infants, children, and adolescents without pre-existing liver disease. In this update, we summarize recently published contributions to the PALF literature, with particular emphasis on emerging recognition of the role of immune dysregulation in PALF of indeterminate etiology and its relevance to new opportunities for identification of novel treatments.

Wilson Disease in Children

The silver anniversary of the discovery of the Wilson disease gene ATP7B was a few years ago, and we continue to make progress both in our understanding of copper transport using animal models, as well as establishing earlier diagnosis by availing of genetic testing. Wilson disease is multisystemic and the hepatic manifestations are seen more frequently in childhood, whereas neurologic manifestations are more common in adults; clinical presentation may range from subtle changes to end-stage liver disease with or without encephalopathy as well as neuropsychiatric manifestations. Molecular diagnosis and genetic counseling is important. Treatment remains with zinc and chelating agents such as D-penicillamine and trientine but newer agents and gene therapy are currently in clinical trials. Liver transplantation becomes necessary when medical therapy is not enough.

Recent Insights into Pediatric Primary Sclerosing Cholangitis

This article reviews recent literature on the pathogenesis, presentation, diagnosis, comorbidities, natural history, and management of pediatric primary sclerosing cholangitis (PSC). The authors shed light on the role of genetic and environmental factors in PSC, although recognize the limitations in the understanding of PSC pathogenesis. They reflect on presenting disease phenotypes, including the association with inflammatory bowel disease and frequent histologic presence of autoimmune hepatitis features. The current lack of effective medications is discussed, and disease complications and prognosis are described. Finally, the authors highlight available evidence while acknowledging the paucity of prospective pediatric data.

Pediatric Liver Transplantation

Liver transplantation (LT) for children results in excellent short- and long-term patient and graft survival. LT is a lifesaving procedure in children with acute or chronic liver disease, hepatic tumors, and select genetic metabolic diseases in which it can significantly improve quality of life. In this article, the authors discuss the unique aspects of pediatric LT, including the indications, appropriate patient selection and evaluation, allocation of organs, transplant surgery including the use of variant grafts, posttransplant care including immunosuppression management, prognosis, and transition of care.
Malnutrition in children with chronic cholestasis is a prevalent issue and a major risk factor for adverse outcomes. Fat soluble vitamin (FSV) deficiency is an integral feature of cholestatic disease in children, often occurring within the first months of life in those with neonatal cholestasis and malnutrition. This review focuses on FSVs in cholestasis, with particular emphasis on a practical approach to surveillance and supplementation that includes approaches that account for differing local resources. The overarching strategy suggested is to incorporate recognition of FSV deficiencies in cholestatic children in order to develop practical plans for close monitoring and aggressive FSV repletion. Routine attention to FSV assessment and supplementation in cholestatic infants will reduce long periods of inadequate levels and subsequent adverse clinical sequelae.